

What is claimed is:

1. An antisense molecule targeted to a nucleic acid molecule encoding human APPL, wherein said antisense molecule is complementary to an expression controlling sequence of said APPL encoding nucleic acid molecule, and upon binding to said APPL nucleic acid inhibits expression of APPL protein.
2. The antisense molecule of claim 1 which is an antisense oligonucleotide.
3. The antisense oligonucleotide of claim 2 selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 2 and SEQ ID NO: 4.
4. The antisense oligonucleotide of claim 3 having the sequence of SEQ ID NO:1, which is 5' - TCCCCGGCATCGTGGCGG - 3'.
5. The antisense oligonucleotide of claim 3 having the sequence of SEQ ID NO: 2, which is 5' - GACCTTGTCTGCGGGC - 3'.
6. The antisense oligonucleotide of claim 3 having the sequence of SEQ ID NO: 4, which is 5' - GGGCAGCTTGTCGATCCCCGGCATCGTGGCGG - 3'.
7. The antisense oligonucleotide of claim 2, wherein said antisense oligonucleotide induces apoptotic cell death in human cells.
8. The antisense oligonucleotide of claim 2, wherein said antisense oligonucleotide comprises at least one modified internucleoside linkage.

9. The antisense oligonucleotide of claim 8,  
wherein said modified internucleoside linkage is a  
phosphorothioate linkage.

5           10. The antisense oligonucleotide of claim 2,  
wherein said antisense oligonucleotide comprises at least  
one modified sugar moiety.

10           11. The antisense oligonucleotide of claim 10,  
wherein said modified sugar moiety is a 2'-O-  
methyloxymethyl sugar moiety;

15           12. The antisense oligonucleotide of claim 2,  
wherein said antisense oligonucleotide comprises at least  
one modified base.

            13. The antisense oligonucleotide of claim 12,  
wherein said modified base is a 5-methylcytosine.

20           14. A method of modulating the expression of APPL  
in human cells or tissues comprising contacting said  
cells or tissues with the antisense molecule of claim 1  
in an amount sufficient to inhibit expression of APPL.

25           15. A method for controlling the expression of APPL  
in human cells, said method comprising:

            a) providing an antisense oligonucleotide  
selected from the group consisting of SEQ ID NO: 1, SEQ  
ID NO: 2 or SEQ ID NO: 4, which hybridizes to an  
30           expression-controlling sequence of a nucleic acid  
molecule that encodes APPL; and

            b) administering said antisense oligonucleotide  
to said human cells in an amount sufficient to control  
expression of said APPL, whereby said antisense  
35           oligonucleotide enters said cells expressing APPL and

binds specifically to the expression-controlling sequence of said nucleic acid molecule encoding APPL thereby inhibiting APPL expression.

5           16. The method according to claim 15, wherein said human cells are selected from the group consisting of skeletal muscle, heart, ovary, and pancreas.

10           17. The method according to claim 15, wherein administration of said antisense oligonucleotide induces apoptotic cell death in said human cell.

15           18. The method according to claim 15, wherein said antisense oligonucleotide is an antisense oligonucleotide analog.

            19. The antisense oligonucleotide of claim 2, wherein said antisense oligonucleotide is encoded by DNA.

20           20. A vector comprising the DNA which encodes the antisense oligonucleotide of claim 19.

25           21. A method of treatment for human malignancy due to the expression of an aberrant APPL protein in a patient requiring such treatment, said method comprising delivery of an antisense oligonucleotide of claim 3 in an amount sufficient to control expression of said protein.

30           22. The method of claim 21, further comprising administration of at least one additional anti-cancer agent selected from the group consisting of cisplatin, carboplatin, herceptin, taxol, taxane derivatives, cyclophosphamide, methotrexate, vincristin, and etoposide.

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23. A pharmaceutical preparation for treating human malignancy due to the expression by cells of an aberrant APPL protein, comprising an antisense APPL oligonucleotide in a biologically compatible medium.

24. A pharmaceutical preparation according to claim 23, wherein said antisense oligonucleotide comprises the sequence of SEQ ID NO:1, which is 5'- TCCCCGGCATCGTGGCGG - 3'.

25. A pharmaceutical preparation according to claim 23, wherein said antisense oligonucleotide comprises the sequence of SEQ ID NO:2, which is 5' - GACCTTGTCTGCGGGC - 3'.

26. A pharmaceutical preparation according to claim 23, wherein said antisense oligonucleotide comprises the sequence of SEQ ID NO:4, which is 5' - GGGCAGCTTGTCGATCCCCGGCATCGTGGCGG - 3'.

27. A pharmaceutical preparation according to claim 23, which further comprises at least one targeting agent for improving delivery of said antisense oligonucleotide to said cells expressing said protein.

28. A pharmaceutical preparation according to claim 27, wherein said at least one targeting agent comprises a lipid.

29. A pharmaceutical preparation according to claim 23, wherein said antisense oligonucleotide is encapsulated in a lipid vesicle.

30. The pharmaceutical preparation according to claim 23, wherein said antisense oligonucleotide is

selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 2 and SEQ ID NO: 4, and is an analog having a modified internucleotide linkage.

5           31. The pharmaceutical preparation of claim 30, further comprising at least one additional anti cancer agent.

10           32. The pharmaceutical preparation of claim 31, wherein said anti-cancer agent is selected from the group consisting of cisplatin, carboplatin, herceptin, taxol, taxane derivatives, cyclophosphamide, methotrexate, vincristin, and etoposide.

15           33. The pharmaceutical preparation of claim 23, wherein said antisense APPL oligonucleotide is encoded in a vector.

20           34. A double stranded RNA molecule targeted to a nucleic acid molecule encoding human APPL, wherein said double stranded RNA molecule inhibits expression of APPL protein upon entry into a cell comprising APPL encoding nucleic acids.

25           35. The double stranded RNA molecule of claim 34, wherein said double stranded RNA molecule is an siRNA.

30           36. The double stranded RNA molecule of claim 34, wherein said double stranded RNA molecule is an shRNA.

          37. An siRNA molecule as claimed in claim 35, having the sequence of SEQ ID NO: 6.

35           38. An shRNA molecule as claimed in claim 36, having the sequence of SEQ ID NO: 8.

39. A method of modulating the expression of APPL in human cells or tissues comprising contacting said cells or tissues with the siRNA molecule of claim 35 in an amount sufficient to inhibit expression of APPL.

40. A method of modulating the expression of APPL in human cells or tissues comprising contacting said cells or tissues with the shRNA molecule of claim 36 in an amount sufficient to inhibit expression of APPL.

41. A method for controlling the expression of APPL in human cells, said method comprising:

a) providing a siRNA molecule of SEQ ID NO: 6;  
and

b) administering said siRNA molecule to said humans cells in an amount sufficient to control expression of said APPL, whereby said siRNA molecule enters said cells expressing APPL and inhibits APPL expression.

42. The method according to claim 41, wherein said human cells are selected from the group consisting of skeletal muscle, heart, ovary, and pancreas.

43. A method for controlling the expression of APPL in human cells, said method comprising:

a) providing a shRNA molecule of SEQ ID NO: 8;  
and

b) administering said siRNA molecule to said humans cells in an amount sufficient to control expression of said APPL, whereby said siRNA molecule enters said cells expressing APPL and inhibits APPL expression.

44. The method according to claim 43, wherein said human cells are selected from the group consisting of skeletal muscle, heart, ovary, and pancreas.

5           45. A method for controlling the expression of APPL in human cells, said method comprising:

          a) providing a vector encoding an siRNA molecule of SEQ ID NO: 6; and

          b) administering said vector to said humans  
10 cells in an amount sufficient to control expression of said APPL, whereby said vector enters said cells expressing APPL and inhibits APPL expression.

46. The method according to claim 45, wherein said  
15 human cells are selected from the group consisting of skeletal muscle, heart, ovary, and pancreas.

47. A method for controlling the expression of APPL in human cells, said method comprising:

20           a) providing a vector encoding an shRNA molecule of SEQ ID NO: 8; and

          b) administering said vector to said humans  
cells in an amount sufficient to control expression of said APPL, whereby said vector enters said cells  
25 expressing APPL and inhibits APPL expression.

48. The method according to claim 47, wherein said human cells are selected from the group consisting of skeletal muscle, heart, ovary, and pancreas.

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49. A method of treatment for human malignancy due to the expression of an aberrant APPL protein in a patient requiring such treatment, said method comprising delivery of a siRNA molecule of claim 35 in an amount  
35 sufficient to control expression of said protein.

50. The method of claim 49, further comprising  
administration of at least one additional anti-cancer  
agent selected from the group consisting of cisplatin,  
carboplatin, herceptin, taxol, taxane derivatives,  
5 cyclophosphamide, methotrexate, vincristin, and  
etoposide.

51. A method of treatment for human malignancy due  
to the expression of an aberrant APPL protein in a  
10 patient requiring such treatment, said method comprising  
delivery of a shRNA molecule of claim 36 in an amount  
sufficient to control expression of said protein.

52. The method of claim 51, further comprising  
15 administration of at least one additional anti-cancer  
agent selected from the group consisting of cisplatin,  
carboplatin, herceptin, taxol, taxane derivatives,  
cyclophosphamide, methotrexate, vincristin, and  
etoposide.

20 53. A pharmaceutical preparation for treating human  
malignancy due to the expression by cells of an aberrant  
APPL protein, comprising an APPL siRNA in a biologically  
compatible medium.

25 54. The pharmaceutical preparation according to  
claim 53, wherein said siRNA comprises the sequence of  
SEQ ID NO:6.

30 55. The pharmaceutical preparation according to  
claim 54, which further comprises at least one targeting  
agent for improving delivery of said siRNA to said cells  
expressing said protein.



56. The pharmaceutical preparation according to claim 55, wherein said at least one targeting agent comprises a lipid.

5 57. The pharmaceutical preparation according to claim 56, wherein said siRNA is encapsulated in a lipid vesicle.

10 58. The pharmaceutical preparation of claim 54, further comprising at least one additional anti cancer agent.

15 59. The pharmaceutical preparation of claim 58, wherein said anti-cancer agent is selected from the group consisting of cisplatin, carboplatin, herceptin, taxol, taxane derivatives, cyclophosphamide, methotrexate, vincristin, and etoposide.

20 60. The pharmaceutical preparation of claim 53, wherein said siRNA is encoded in a vector.

25 61. A pharmaceutical preparation for treating human malignancy due to the expression by cells of an aberrant APPL protein, comprising an APPL shRNA in a biologically compatible medium.

30 62. The pharmaceutical preparation according to claim 61, wherein said shRNA comprises the sequence of SEQ ID NO: 8.

35 63. The pharmaceutical preparation according to claim 62, which further comprises at least one targeting agent for improving delivery of said shRNA to said cells expressing said protein.

64. The pharmaceutical preparation according to claim 63, wherein said at least one targeting agent comprises a lipid.

5           65. The pharmaceutical preparation according to claim 64, wherein said shRNA is encapsulated in a lipid vesicle.

10           66. The pharmaceutical preparation of claim 61, further comprising at least one additional anti cancer agent.

15           67. The pharmaceutical preparation of claim 66, wherein said anti-cancer agent is selected from the group consisting of cisplatin, carboplatin, herceptin, taxol, taxane derivatives, cyclophosphamide, methotrexate, vincristin, and etoposide.

20           68. The pharmaceutical preparation of claim 61, wherein said shRNA is encoded in a vector.